LYMErix
Lyme Disease Vaccine (Recombinant OspA)

Post-licensure safety assessment

R. Platt, M.D., MSc
Professor at Harvard Medical School

Surveillance of safety after immunization with Lyme vaccine in the practice setting

Lyme 025 - A Cohort Study

Objectives

- **Primary:**
  Evaluate whether exposure to Lymerix is a risk factor for new onset inflammatory arthropathy.
- **Secondary:**
  Evaluate whether exposure is a risk factor for Lyme disease, treatment resistant Lyme disease, rheumatoid arthritis, some neurologic diseases, allergic events, and death.

Study design

- Prospective cohort study of HMO members immunized as part of routine medical care.
- Vaccinees identified through automated claims and automated medical records.
- Comparison group of non-recipients matched by age, sex, medical practice.
- Passive, uniform, surveillance for 4+ years:
  - screening of automated inpatient/outpatient claims,
  - blinded review of selected full text medical records,
  - link to national death index.

Advantages of HMOs for epidemiologic studies

- Can observe safety under usual practice conditions, involving unselected populations.
- HMOs have data about their members, their health status, and their care.
- Record linkage allows relatively complete, largely passive, surveillance.
- Passive surveillance avoids many types of bias.

Relevant studies in HMOs

- Vaccine safety datalink (CDC)
- Center for Education and Research in Therapeutics (CERTs) (AHRQ and FDA)
- Cancer Research Network (NIH)

Setting

- Harvard Pilgrim Health Care, a non-profit, major teaching affiliate of Harvard Medical School.
- Starting in 2001:
  HealthPartners (Minnesota)
  Tufts Health Plan (Massachusetts)

Investigators

- Richard Platt, M.D., M.Sc.
  - Professor, Harvard Medical School
  - Principal investigator, CDC Vaccine Safety Datalink site
  - Principal investigator, FDA cooperative agreement to study adverse drug reactions
  - Principal investigator, AHRQ/FDA Center for Education and Research in Therapeutics (CERTs)

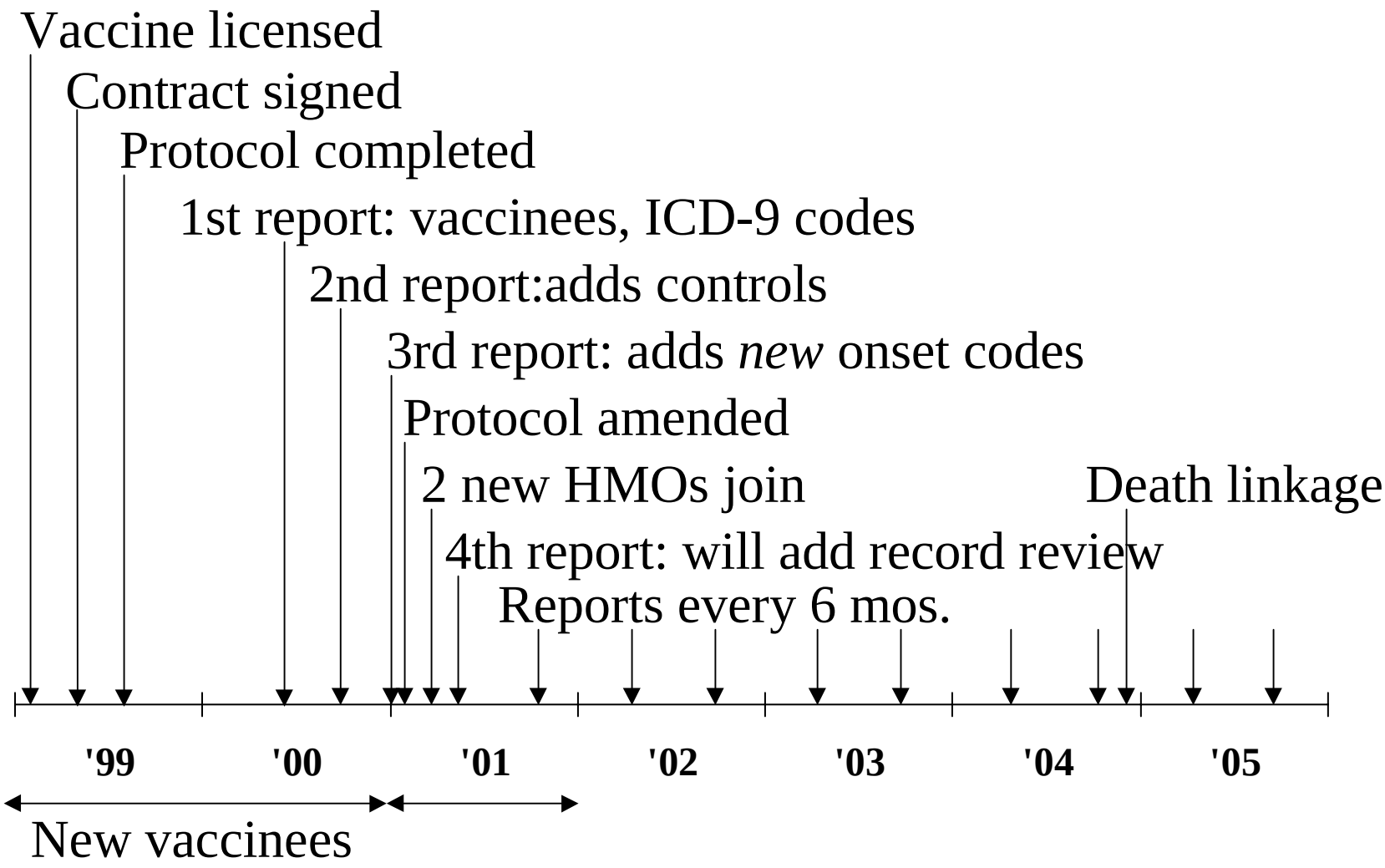
Co-investigators

- K. Arnold Chan, M.D., Sc.D.
  - Harvard School of Public Health
  - Harvard Medical School
- Alexander M. Walker, M.D., Dr.P.H.
  - Harvard School of Public Health
- Matthew H. Liang, M.D., M.P.H.
  - Harvard Medical School
- Nancy Shadick, M.D., M.P.H.
  - Harvard Medical School

Roles/responsibilities

- Protocol developed by investigators with sponsor, in response to FDA input.
- Sponsor interacts with FDA.
- All research activities, including data gathering, analysis, report writing, are conducted solely by the investigators.
- Data owned and controlled by the investigators.

Timeline


Vaccine licensed
Contract signed
Protocol completed
1st report: vaccinees, ICD-9 codes
2nd report:adds controls
3rd report: adds *new* onset codes
Protocol amended
2 new HMOs join
Death linkage
4th report: will add record review
Reports every 6 mos.
'99
'00
'01
'02
'03
'04
'05
New vaccinees

Characterization of vaccinees

- Search automated data files for people with relevant procedure.
- Among these, select continuous HMO members since January 1, 1999.
- Identify diagnosis codes up to 3 years BEFORE vaccination.
- For each report, identify additional immunizations and diagnosis codes after vaccination.
- Blinded review of medical records with codes of interest.

Characterization of controls

- For each vaccinee, identify 3 people in the same practice, with the same sex and age, who were continuous HMO members since January 1, 1999.
- Assign *vaccinee's* immunization dates as referent dates.
- Identify diagnosis codes before referent dates.
- For each report, identify diagnosis codes after referent date.
- Blinded review.

Validity of immunization data

- Review of random sample of medical records showed 99% of automated claims to be accurate.
- Immunization status (yes/no) will be confirmed for all potential cases during chart review.

Confirming new events of interest

- Full text ambulatory and/or hospital records obtained if there is a new diagnosis code of interest.
- First level review by chart abstractor to eliminate events that are clearly not of interest.
- Formal blinded review by rheumatologist, using standardized abstraction form.
- Two rheumatologists -- interobserver variability to be assessed.

Analysis plan

- Incidence rates and rate ratios, crude and stratified.
- Assessment of dose-response relationship.
- Multivariate analysis using proportional hazards, plus Poisson regression for crossovers.
- Exploration for unanticipated potential adverse effects, identified as new codes that occur among more than 5 vaccinees.

Power: assumes 25,000 vaccinated, 75,000 non-vaccinated

Baseline rate	**Power to detect incidence rate ratio of:**		
	1.8	**2**	**2.2**
3 per 10,000	90%	98%	99+%
2 per 10,000	79%	89%	97%
1 per 10,000	50%	65%	78%

Preliminary results

- 2,568 were immunized through 6/30/1999.
- 3,677 were immunized through 11/15/2000.
- 2,787 had 2 or more doses.
- *New* rheumatologic ICD-9 code (not reviewed)
  - Vaccinees 8.5% (218/2,568)
  - Comparators 7.6% (568/7,497)
- Hospitalization with *new* rheumatologic ICD-9 code
  - Vaccinees 0.04% (1/2,568)
  - Comparators 0.9% (7/7,497)

Preliminary conclusions

- HMO based record linkage research is able to identify vaccinees reliably.
- First assignment of rheumatologic diagnosis *codes* is approximately equally common in vaccinees and comparators.
  - Most probably do not represent outcomes of interest.
- Chart review is necessary to identify new onset conditions of interest.

Current plan

- Continue existing protocol -- add record review
- 2 new HMOs to join in 2001;
  their data is available since 1999.

Contingency plan

- Recompute power/confidence limits based on new totals and observed incidence rates.
- If recruitment is insufficient, consider extending recruitment period or identifying additional HMO collaborator.

Passive post-marketing surveillance

- Vaccine licensed for 2 years; 1.4 million doses distributed
- 984 adverse event reports received by Nov 30, 2000
- Observations:
  - Early onset reactogenicity profile, as reported during clinical development, confirmed. Some of the symptoms reported in the prescribing information for LYMErix appeared to occur concomitantly with early onset after vaccination
  - Hypersensitivity has been reported very rarely

Comparison of Prescribing Information and postmarketing observations - General symptoms -

Prescribing Information

solicited

- Arthralgia
- Fatigue
- Rash

unsolicited (within 30 days)

- Chills/rigors
- Fever
- Influenza-like symptoms
- Myalgia

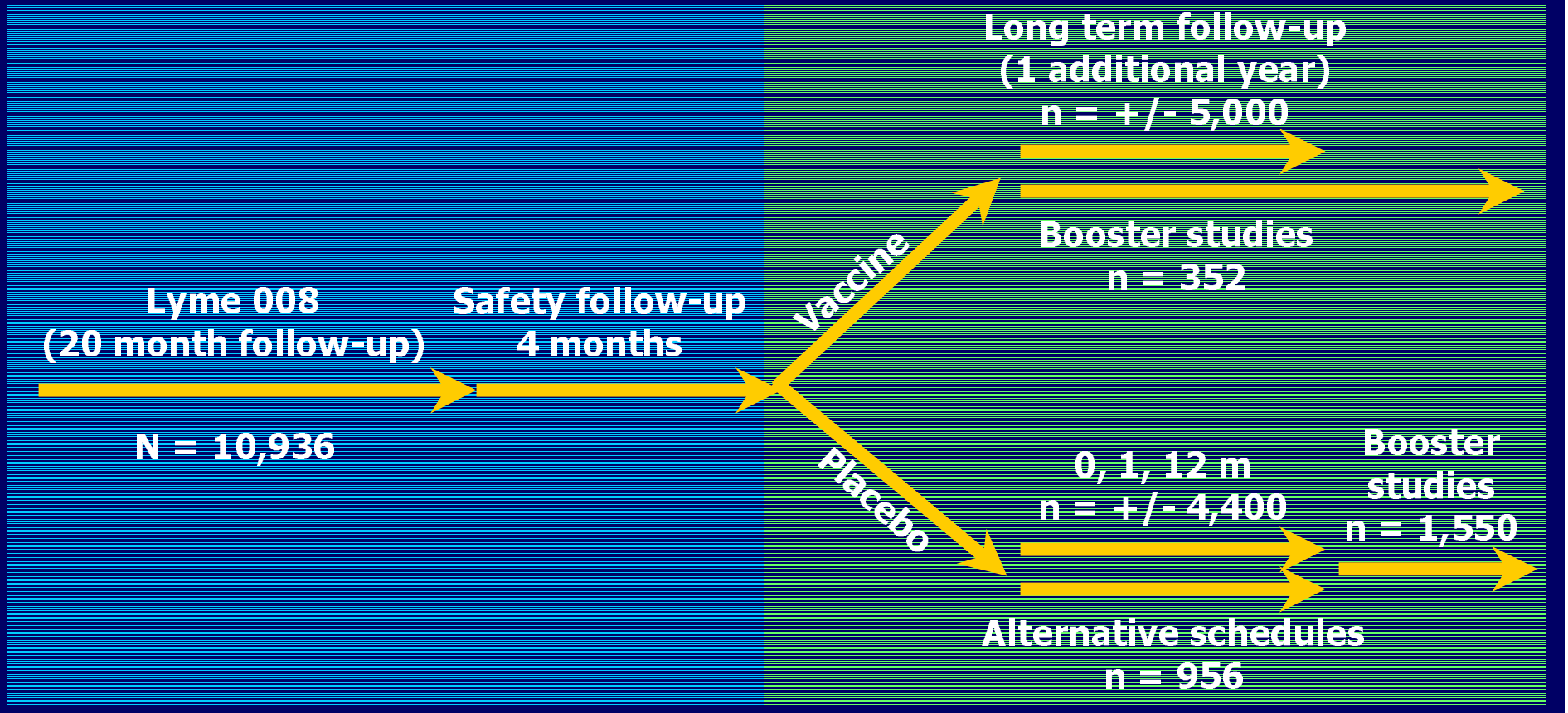
Postmarketing surveillance

- Arthralgia
- Arthrosis (joint swelling or stiffness)
- Fatigue
- Rash
- Rigors
- Fever
- Influenza-like symptoms
- Headache (mostly associated with influenza-like symptoms)
- Myalgia
- Pain

Arthritis

- Evaluation of 70 reports, data lock point Sep 25, 2000
- No evidence that the incidence is higher than in the general population
- No particular clinical pattern identified
- No cluster in time to onset
  - ➨ Arthritis cases reported in postmarketing surveillance not considered to be associated with vaccination
- Data will be reviewed by an independent panel of rheumatology experts

Additional Clinical Trial Experience



Cross-Over of the Efficacy Study Preliminary Results

- Open labeled, cross-over vaccination of Lyme 008 placebo recipients
- n = 3,578
- 0, 1, 12 month schedule
- Unsolicited AE reports via safety postcards
- Similar to the pivotal efficacy study, most frequently reported adverse events were:
  - injection site pain
  - myalgia, arthralgia
  - influenza-like symptoms

Additional Clinical Trial Experience

- Alternative schedules
  - 0, 1, 6 m versus 0, 1, 12 m (Lyme 014) n=400/group
  - 0, 1, 2 + 12 m versus 0, 1, 12 m (Lyme 016) n=500/group
- Booster studies n = 1,800 subjects, up to 6 doses total

- Pediatric population (Lyme 022)
  - 4,000 subjects, 4 - 18 years old
  - 3,000 receiving LYMErix, schedule 0, 1, 12 m

➨ Nature and frequency of AEs were similar to pre-licensure clinical trial experience

LYMErix Vaccinees in Clinical Studies

Pre Licensure Studies	
BLA	**6,478**
Post Licensure Studies	
Cross-Over Efficacy Trial	3,578
Pediatric Studies	1,756
Alternate Schedules	3,063
	8,397
Total Vaccinated Subjects	**14,875**
+ Cohort Study	3,677

Conclusion of Post-Licensure Commitments

- Study on cellular immunity: no evidence of association between vaccination and incidence of inflammatory arthropathy
- No maternal or fetal reproductive toxicity in rats
- Pregnancy registry has been established, no unexpected observation
- Cohort study to assess the safety of LYMErix
  - Lower than the expected number due to the low vaccination rate of the searched population
  - No difference in event codes between vaccinees and control group observed to date

Conclusion of Data from Postmarketing Surveillance and Post-Licensure Studies

- Most frequently reported AEs involve symptoms already described in the prescribing information - in certain individuals, these symptoms are described as occuring concomitantly
- Hypersensitivity has been reported very rarely in postmarketing surveillance
- Arthritis cases observed in postmarketing surveillance not considered to be associated with vaccination
- Post-Licensure studies involving more than 8,000 vaccinees confirm the safety profile observed during development of the vaccine